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NIH Research Contract No. NINDS-N01-NS-3-2380
Sensory feedback signal derivation from afferent neurons

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A. Overall objectives of this research

1. Investigate, in cadaver material, implantation sites for nerve cuff electrodes from which cutaneous and proprioceptive information relevant to the human fingers, hand and forearm could be recorded.
2. Select a suitable animal preparation in which human nerve dimensions and electrode placement sites can be modeled and tested, with eventual human prosthetic applications in mind.
3. Obtain or fabricate nerve cuff electrodes suitable for these purposes.
4. Investigate the possibility of extracting information about contact and slip from chronically recorded nerve activity using the animal models and electrodes from parts 2 and 3. Specifically,
 - a. devise recording, processing and detection methods to detect contact and slip from recorded neural activity in a restrained animal;
 - b. modify these methods as needed to function in an unrestrained animal and in the presence of functional electrical stimulation (FES);
 - c. record activity for periods of at least 6 months and track changes in neural responses over this time.
5. Supply material for histopathological examination from up to 5 cuffed nerves and contralateral controls, from chronically implanted animals.
6. Investigate the possibility of extracting information about muscle force and limb position from chronically recorded neural activity.
7. Cooperate with other investigators of the Neural Prosthesis Program by collaboration and sharing of experimental findings.

B. Objectives that were achieved

Objectives 1, 2, 3 and 4 were fully met and significant progress was achieved. The research accomplished in each year of this contract is summarized in Section F. Results were reported in detail in 12 Quarterly Progress Reports (QPRs), presented at thirteen meetings and published in six abstracts, five refereed communications and one paper, listed in Section E. Three full manuscripts are nearly ready to be submitted for publication and a fourth is in preparation. A patent was obtained for an improved nerve cuff electrode closure mechanism that evolved from our research toward Objective 3 of this contract.

C. Objectives that were not achieved

Objective 5 was only partially met during the period of the contract. Histological samples were removed from cuffed nerves and their contralateral controls from all implanted animals in Years One and Two (NIH 1 - 14; Year Three animals are still under study at the time of preparation of this Final Report). Samples were prepared for light microscopical analysis. The quality of tissue fixation was poor in Year 1 (animals NIH 1 - 8); this was corrected for subsequent animals. The quantitative histological analysis has not been completed. This constitutes the M.Sc. thesis project of a graduate student (D. Crouch) intended to be completed in 1997.

Progress on Objective 6 was modest in extent but its results are encouraging. Two miniature nerve cuffs were implanted on two muscle nerve branches in one cat (NIH-15) and produced good quality joint position-dependent proprioceptive nerve signals that were successfully recorded for over one year. The signal analysis that was carried out was largely qualitative in these preliminary experiments.

D. Recommendations for future research & development

In the period of this contract only single-channel tripolar nerve cuffs were used. In future experiments, the possibility of extracting several channels of information from individual nerves should be thoroughly investigated. Two approaches that warrant investigation are intrafascicular electrodes and multicontact nerve recording cuffs. These recording approaches, combined with high-powered signal analysis methods like machine learning and neural networks analysis, may provide independent information about several sensory sources or modalities simultaneously present in individual nerves. This approach, if successful, is likely to be of great value for the simultaneous control of several output variables or degrees of freedom with FES.

E. Publications supported by this contract

Abstracts

1. Hoffer, J.A., and Strange, K.D., (1996), A State Controller for Functional Electrical stimulation Regulated by Natural Sensory Feedback, poster at Canadian Network of Centres of Excellence Annual Meeting, Ottawa, Ont., May 1996.
2. Strange, K. and Hoffer, J.A., (1995), Cutaneous neural feedback can be used to predict timing of muscle activation in the cat forelimb during locomotion, *Soc. Neuroscience Abstr.* 21: 419.
3. Hoffer, J.A., Strange, K.D., Kallesøe, K., and Valenzuela, I., (1995), Development of Implantable Neural Interface Technologies, poster at Canadian Network of Centres of Excellence Annual Meeting, Ottawa, Ont., May 1995.
4. Hoffer, J.A., Kallesøe, K., Strange, K., and Schindler, S., (1994), Sensory Feedback Signal Derivation From Afferent Neurons, poster at Canadian Network of Centres of Excellence Annual Meeting, Ottawa, Ont., May 1994.
5. Strange, D. Crouch, K. Kallesoe, M. El Mouldi, S. Schindler, I. Valenzuela, D. Viberg, and J.A. Hoffer., (1994), Sensory Feedback Signal Derivation from Afferent Neurons, abst. in *Abstr. Neural Prostheses: Motor Systems IV Conf.*, Deer Creek, Ohio, p. 35, July 1994.
6. Hoffer, J.A., Kallesøe, K., El Mouldi, M., Schindler, S., Strange, K., and Viberg, D., (1993), Sensory Feedback Signal Derivation From Afferent Neurons for Control of FES, poster at Canadian Network of Centres of Excellence Annual Meeting, Ottawa, Ont., May 1993.

Refereed communications

1. Kostov, A., Strange, K., Stein, R.B., and Hoffer, J.A., (1996), Adaptive Logic Networks in EMG-Prediction from Sensory Nerve Signals Recorded in the Cat's Forelimb During Walking. *Physiology Canada*
2. Strange, K. and Hoffer, J.A., (1996), FES state controller using natural sensory feedback, accepted for *Proc. Can. Soc. Biomech.*, Vancouver, Canada.
3. Strange, K. and Hoffer, J.A., (1995), Using cutaneous neural signals to predict cat forelimb muscle activity during walking, in *Proc. of IEEE SMC*, Vancouver, Canada, Oct. 1995, vol.2, pp. 1199-1204.
4. Christensen, P.R. and Hoffer, J.A., (1995) An eight-channel biphasic stimulator for functional electrical stimulation. *Proc. Rehab. Eng. Soc. N. Amer. Ann. Conf.*, 375-377.

5. Strange K.D., Hoffer J.A., Kallesøe K., Schindler S.M., and Crouch D.A., (1995), Long-term stability of nerve cuffs implanted in the cat forelimb, *Proc. Rehab. Eng. Soc. N. Amer. Ann. Conf.*, 372-374.

Full papers published

1. Hoffer, J.A., Stein, R.B., Haugland, M., Sinkjær, T., Durfee, W.K., Schwartz, A.B., Loeb, G.E. and Kantor, C., (1996), Neural signals for command control and feedback in functional neuromuscular stimulation, *J. Rehab. Res. & Dev.*, Vol. 33, pp. 145-157.

Full papers in preparation

1. Strange, K.D., Kallesøe, K., and Hoffer, J.A., Long-term stability of signals recorded from cat forelimb nerves with cuff electrodes. To be submitted to *IEEE trans. BME*.

Nerve cuff electrodes were implanted on two of the Median, Ulnar, and/or Radial nerves in cat forelimbs. Conventional cuff recording electrodes utilizing closing sutures were used in a first series of eight cats. Nerve cuffs of a novel design were implanted in a second series of six implants. The cats were group-housed and could jump and move about freely in a holding room equipped with shelves up to 1.5 m high. The viability and stability of the nerves and recording devices were periodically evaluated by monitoring evoked compound action potentials (CAPs) and device impedances for at least six months. The nerve cuff design used in the second series had more stable CAPs and impedances than the nerve cuff design used in the first series. This study demonstrates that stable neural recordings are possible for extended periods in freely moving animals. Our results lend support to the long-term use of nerve cuff recording electrodes for the control of functional electrical stimulation systems and neural prostheses in human applications.

2. Strange, K.D. and Hoffer, J.A., Sensory signals from cat paw receptors during walking: applicability as state controller feedback for FES. To be submitted to *IEEE trans. BME*.

In this study we recorded natural sensory nerve signals of primarily cutaneous origin in the forelimbs of cats during walking on a motorized treadmill, using chronically implanted nerve cuff or patch electrodes on the Median, Ulnar, and Radial nerves. EMG activity from four forelimb muscles, Palmaris Longus, Flexor Carpi Ulnaris, Extensor Carpi Ulnaris, and Abductor Pollicis Longus, was also recorded during walking to correlate sensory ENG activity with EMG activity during the step cycle. Features in the ENG signals that were related to paw contact and lift-off were detected by a state controller model and used to predict the timing of the activity of a forelimb muscle for a variety of walking conditions. The accuracy with which EMG timing information could be predicted from the cutaneous ENG signals recorded during walking suggests that natural sensory signals may be implemented as a source of feedback for closed-loop control of functional electrical stimulation (FES).

3. Strange, K.D. and Hoffer, J.A., Forelimb sensory nerve signals provide reliable state controller feedback for FES during cat walking. To be submitted to *IEEE trans. BME*.

A real-time FES state controller was designed that utilized sensory nerve cuff signals from the cat forelimb to control the timing of stimulation of the Palmaris Longus (PalL) muscle during walking on the treadmill. Sensory nerve signals from the Median and Superficial Radial nerves provided accurate, reliable feedback related to foot contact and lift-off which, when analyzed with single threshold Schmitt triggers, produces valuable state information regarding the step cycle. The study involved three experiments: prediction of the timing of muscle activity in an open-loop configuration with no stimulation, prediction of the timing of muscle activity in a closed-loop configuration that included stimulation of the muscle over natural PalL EMG, and temporary paralysis of selected forelimb muscles coupled with the use of the state controller to stimulate the PalL in order to return function to the anesthetized limb. The FES state controller was tested in a variety of walking conditions, including different treadmill speeds and slopes. The results obtained in these different conditions demonstrate that nerve cuff signals can provide a reliable source of feedback to FES systems used for restoration of movement in humans.

4. Kostov, A., Strange, K., Stein, R.B., and Hoffer, J.A. (1996), Artificial neural networks application in EMG-prediction using sensory nerve signals recorded in the cat's forelimb during walking, in preparation. Intended for *IEEE trans. BME*.

We evaluated the potential use of sensory nerve signals as sensory feedback in closed-loop control systems for FES-assisted walking. We focused on the control of flexor/extensor actions of the intact cat's forelimb, represented by the EMG signals recorded using intramuscular electrodes from two flexor muscles (Palmaris Longus and Flexor Carpi Ulnaris) and two extensor muscles (Extensor Carpi Ulnaris and Abductor Pollicis Longus) during walking on a motorized treadmill. Sensory signals were simultaneously recorded in the cat's forelimb from Ulnar and Median or Ulnar and Radial nerves using cuff electrodes. These nerves were selected because they carry a majority of the cutaneous and some proprioceptive sensation arising from the distal forelimb. The use of sensory nerve signals in predicting EMG signals was seen as an important step toward designing controllers which will produce more natural movements of paralyzed limbs in people with spinal cord injuries. To extract the relationship between sensory nerve signals and EMG signals, we applied Adaptive Logic Networks (ALNs), a type of artificial neural networks for supervised learning. These relationships were extracted in the training phase and stored in the form of ALN neural trees. They were then used to predict EMG signals when only the sensory nerve signals were provided. For practical applications in neuroprosthesis design, it is of particular interest to provide good generalization over long periods of time and transferability from one subject to another. Generalization was assessed using the coefficient of determination (RSQ) for the predicted and the original EMG signals. In the present study we achieved very good ALN learning and generalization over the same walking session, even when we used only one of the sensory signals or data from only one gait cycle for training. Current efforts are focused on generalization over longer periods of time.

Patents awarded

1. Kallesøe, K., Hoffer, J.A., Strange, K., Valenzuela, I., (1996) Implantable cuff having improved closure. U.S. Patent 5,487,756, awarded Jan. 30, 1996.

F. Summary of research performed during contract period

Year One

1. Human Cadaver Studies

Three human cadavers were examined for forearm and hand nerves as possible sites for instrumentation with nerve cuffs. The examination included cutaneous and proprioceptive nerves, and the nerve diameters and available free lengths were recorded and summarized in terms of possible nerve cuff applications (QPR#1).

The human cadaver data suggested that similarities between human digital nerve sizes and functions and cat forelimb cutaneous nerve sizes and functions validated the selection of using the cat as the animal model for the contract.

2. Animal Implants

<u>Subject</u>	<u>Instrumented Nerves</u>	<u>Types of Nerve Cuffs</u>
NIH-1	Median and Ulnar	Suture type, tripolar
NIH-2	Median and Ulnar	Suture type, tripolar
NIH-3	Median and Ulnar	Suture type, tripolar
NIH-4	Median and Ulnar	Suture type, tripolar
NIH-5	Median and Ulnar	Suture type, tripolar
NIH-6	Median and Ulnar	Suture type, tripolar
NIH-7	Median and Ulnar	Suture type, tripolar
NIH-8	Median and Ulnar	Suture type, tripolar

Experiments Under Anesthesia:

All cats in Year One were implanted with distal recording cuffs and proximal stimulating cuffs. All implanted cuffs in Year One were of the traditional suture-type closing method. In addition, each cat was instrumented with buried EMG electrodes in the Palmaris Longus muscle.

The cutaneous innervation fields of all instrumented nerves were determined under anesthesia by monitoring the nerve signals during both mechanical and electrical stimulation of the paw and digits.

Cat NIH-1 had to be terminated after 101 days due to breakage of cuff lead wires (QPR#4). The nerve compound action potentials (CAPs) in cats NIH-2 to NIH-8 were monitored at periodic intervals for at least 180 days to evaluate the condition of the instrumented nerves and the condition of the devices (QPR#2). Data for CAP peak-to-peak amplitudes and conduction latencies recorded under anesthesia were normalized and averaged to produce summary results of 14 instrumented nerves (QPR#5).

Averaged CAP amplitudes and conduction latencies showed high degrees of stability over 180 days. In addition, nerve cuff impedances were monitored under anesthesia and showed a high degree of stability over 180 days.

Experiments with the awake cat:

Cats NIH-2 to NIH-7 were recorded walking on a treadmill to determine what signals could be recorded during voluntary activity and the what type of information was contained in the nerve cuff signals that was related to the step cycle.

Preliminary reaching and grasping data were obtained in experiments where the cat manipulated passive devices including strings and a spring-loaded 1-D joystick.

Setbacks in Year One:

We experienced a number of cases of snagged and broken cuff electrode wires, where the cats accessed the wires at the backpack in the process of scratching (QPR#5). These issues were addressed by improving the backpack sutures and utilizing a fabric belly band which restricted access to the backpack (QPR#6).

Year Two

1. Animal Implants

<u>Subject</u>	<u>Instrumented Nerves</u>	<u>Types of Nerve Cuffs</u>
NIH-9	Median and Ulnar	baton-type, tripolar
NIH-10	Median and Ulnar	baton-type, tripolar
NIH-11	Median and Ulnar	baton-type, tripolar
NIH-12	Median and Radial	baton-type, tripolar
NIH-13	Radial and Ulnar	baton-type, tripolar
NIH-14	Radial and Ulnar	baton-type, tripolar

Experiments Under Anesthesia:

All cats in Year Two were implanted with distal recording cuffs and proximal stimulating cuffs. All implanted recording cuffs in Year Two were of the baton-type closing method, a new closing method that was patented by Kallesøe et al. (1996) (QPR#4). In addition, each cat was instrumented with patch or epimysial EMG electrodes on the Palmaris Longus, Flexor Carpi Ulnaris, Extensor Carpi Ulnaris and Abductor Pollicis Longus muscles (QPR#5).

CAPs were monitored periodically for at least 180 days in all six Year Two cats. The averaged CAP conduction latency and amplitudes exhibited even greater long term stability than that observed in the Year One implants (QPR#8). Nerve and cuff stability results for Years One and Two are discussed in the manuscript by Strange, Kallesøe, and Hoffer (1996).

Experiments in the awake cat:

All six cats were recorded while walking on the powered treadmill at a variety of treadmill speeds (0.5 to 1.25 m/s) and slopes ($\pm 10\%$). Nerve cuff signals were analyzed for EMG contamination from active muscles near the implanted cuffs and in terms of timing information related to the step cycle (QPR#7, 9, and 10). We found that all nerve cuff signals were systematically modulated during the step cycle, with largest ENG activity occurring during transition phases such as paw contact and paw lift-off.

A model state controller for possible FES applications was developed to examine the use of cutaneous nerve cuff signals to detect events in the step cycle and produce a control signal related to the timing of the step cycle (QPR#9). The model was evaluated with data from different cats over time as well as different walking conditions. The accuracy of the model suggested that useful timing information can be reliably obtained from cutaneous nerve cuff recordings during walking (Strange and Hoffer, 1996).

A collaborative project involving machine learning techniques and adaptive logic networks was initiated with Drs. Kostov and Stein at the University of Alberta. The goal was to use adaptive logic networks to learn from patterns of nerve cuffs signals during walking and predict the amplitude modulations of associated EMG signals (Kostov et al., 1996 and in preparation).

Year Three

1. Animal Implants

<u>Subject</u>	<u>Instrumented Nerves</u>	<u>Types of Nerve Cuffs</u>
NIH-15	Median and Radial FDP and EDL nerves	baton-type, tripolar hybrid patch/ cuff, tripolar
NIH-16	Median and Radial Proximal Median	baton-type, tripolar blocking cuff
NIH-17	Median and Radial Proximal Median	baton-type, tripolar blocking cuff

Experiments Under Anesthesia:

Three cats in Year Three were instrumented on the Radial and Median nerves with tripolar recording cuffs including the baton-type closing method. CAPs were monitored periodically to determine the condition of the instrumented nerves and the implanted devices, both of which showed stability agreeing with the results of the Year Two implants. At the time of preparing this report, all three Year Three cats were still under study with the longest (NIH-15) now at over 1 year post-implant.

NIH-15 was also instrumented with two miniature nerve cuffs (~0.5 mm ID, 5 mm long) on the small nerve branches to the FDP and Extensor Digitorum Longus muscles. In experiments under anesthesia, mechanical perturbations of wrist and digit flexion and extension produced distinct, alternating modulations of the FDP and EDL nerve cuff signals (QPR#11). The signals appeared to be position and velocity dependent, and suggested that useful proprioceptive feedback signals from individual muscles may be obtainable in the awake cat during voluntary activity.

NIH-16 and NIH-17 were instrumented with a proximal Median nerve blocking cuff which was designed to act as a reservoir around the nerve to hold local anesthetic introduced through a catheter connected to the backpack. The local anesthetic was used to produce a Median nerve conduction block to effectively paralyze muscles innervated by the Median nerve below the block and to remove sensory information from reaching higher centres. Experiments under general anesthesia showed that the blocking cuff could successfully block conduction of the Median nerve.

Experiments under anesthesia also included a determination of recruitment properties of instrumented forelimb muscles for subsequent use in FES experiments. Stimulation parameters investigated included current amplitude, pulse width, and stimulation frequency.

Experiments in the awake cat during walking:

A real-time FES state controller was designed based on the model developed in Year Two. The Median and Radial nerves supplied useful timing information and triggered the state transitions of the FES controller. We demonstrated that cutaneous nerve activity could be used to control the state of a real-time FES state controller and produce a return of function to the wrist during temporary paralysis of wrist flexors effected by a Median nerve conduction block (Strange and Hoffer, 1996). These experiments formed part of an M.A.Sc. thesis completed by Kevin Strange in April 1996.

Experiments in the awake cat during reaching and grasping:

A 2-D computer controlled joystick for a reaching and grasping task (QPR#12) was developed initially by D. Viberg and completed by Dr. Y. Chen. The cat sits in a restraining jacket and reaches with its instrumented limb for the joystick, pulls the joystick towards its mouth, and receives a food reward for a successful trial. The joystick acts as a spring-loaded device with the computer controlling the stiffness of the motors in both dimensions. Load or lateral slip perturbations can be introduced to the joystick that trigger responses from the cat.

Cutaneous nerve cuff recordings from all three Year Three cats on the forelimb reaching and grasping task have been examined for useful information pertaining to timing of contact and release and timing of perturbations. Control strategies for use in a FES system to return function to the wrist following Median nerve conduction block are being produced which utilize timing information available in the cutaneous nerve cuff recordings. At the time of writing this report, off-line analysis of the nerve cuff signals has been completed and the design of a real-time FES state controller has been initiated. This research at SFU will constitute an M.Sc. thesis by Morten Hansen, a visiting graduate student from Aalborg Univ., Denmark jointly supervised by J.A. Hoffer and M. Haugland.